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EDITORIAL COMMENT

PET Imaging of Leukocytes in Patients With Acute Myocardial Infarction*

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Myocardial infarction (MI) remains one of the most common health emergencies, and a sizable fraction of acute MI patients develop subsequent complications (1). Despite guideline-adherent therapy, post-MI heart failure occurs, motivating efforts to identify patients at risk and to develop novel therapeutic strategies. Increasingly, cardiologists are looking at the immune system's role in the repair of the ischemic heart, and systemic inflammatory networks that could be targeted to oppose progression of ischemic heart disease. Two hurdles block our path to new therapeutics: the heterogeneity of the immune response in individual patients, and the detrimental as well as

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protective consequences of immune system activation on the organism. These hurdles may be overcome with improved surveillance of immune cell activity in cardiovascular organs, as this would enable patient selection and therapeutic monitoring. Similar strategies are being pursued in oncology where specific types of cancer are treated with personalized therapeutics, and increasingly, drug development is guided by tailored companion-imaging approaches. In this issue of *iJACC*, 2 articles introduce a promising positron-emission tomography (PET) imaging approach to monitor the presence of immune cells in the acute infarct of patients with ischemic heart disease (2,3).

Both studies investigate an imaging agent that binds to the chemokine receptor CXCR4. The small molecule PET tracer ^{68}Ga-pentixafor has advanced into human studies, mostly driven by cancer imaging applications (4), where the imaging agent may report on therapeutics that interfere with CXCR4 signaling (5). CXCR4 and its ligand SDF-1 are widely expressed in the steady-state. Among other functions, the chemokine/chemokine receptor pair regulates the activity and migration of hematopoietic stem cells and leukocytes, including neutrophils and monocytes. The latter innate immune cells promote ischemic heart disease and are central regulators of infarct healing and regeneration (1). After MI, inflammatory neutrophils and monocytes are released from the bone marrow and spleen, where they are produced from hematopoietic stem and progenitor cells (**Figure 1**). Interestingly, post-MI proliferation and migration of hematopoietic progenitor cells is regulated by CXCR4 (6). Once recruited to the infarct, phagocytic immune cells remove dead stromal cells. After 3 to 4 days, inflammation begins to resolve, while neutrophil numbers decline and macrophages assume less inflammatory functions. This transition from inflammation to resolution supports repair; however, if it is delayed, for instance, due to oversupply of inflammatory immune cells, post-MI remodeling and heart failure are more likely to occur (7). These aspects have been studied in detail on the tissue level in rodents, but blood monocyte levels likewise correlate with outcome in human patients with acute MI (1). To date, it has been difficult to image infarct inflammation in the human heart. One exception is ^{18}F-FDG, which enriches in acute infarcts (8) but suffers from specificity limitations as this tracer may be taken up by cardiomyocytes. Infarct-induced bone marrow proliferation may be assessed by PET imaging after injection the thymidine analog ^{18}F-FLT (9), but this agent is not cell-specific either. Thus, specific imaging agents, which only bind to certain leukocytes and not to stromal cells, are needed.

In a comprehensive study in mice and humans, Thackeray et al. (3) describe that ^{68}Ga-pentixafor

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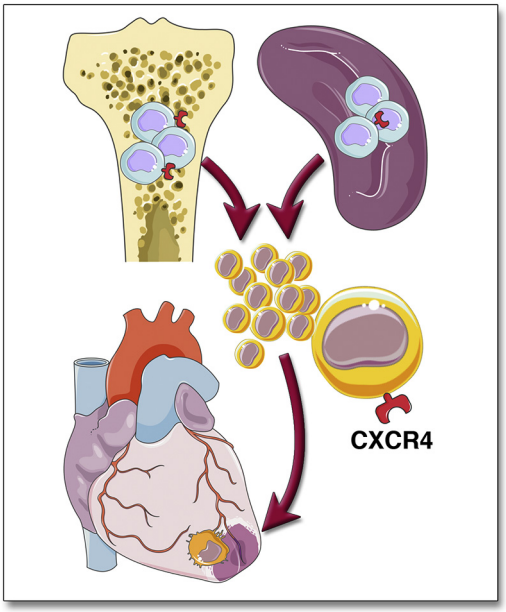
FIGURE 1 Cell Flux and the Imaging Target CXCR4 After Acute Myocardial Infarction



After myocardial infarction, increased hematopoiesis in spleen and bone marrow supplies innate immune cells (neutrophils, monocytes) to the infarct. These cells, and their progenitors in hematopoietic tissues, express CXCR4, a chemokine receptor that serves as an imaging target in the discussed manuscripts.

enriches in acute infarcts. PET signal was higher at earlier times after coronary ligation; was blocked with a CXCR4 inhibitor; and attenuated by application of an angiotensin-converting enzyme (ACE) inhibitor, standard post-MI treatment that was previously shown to attenuate the splenic supply of immune cells to the acute infarct (8). The investigators also report ^{68}Ga-pentixafor PET imaging in 12 patients. The PET signal varied and not all infarcted segments were positive. ^{68}Ga-pentixafor enrichment was low in normal myocardium and highest early after MI and in myocardial segments that were severely damaged (indicated by lowest perfusion on single-photon emission computed tomography, highest scores for delayed Gd enhancement and edema on cardiac magnetic resonance). Tracer uptake in hematopoietic organs was detected, especially in the spleen, and correlated to imaging signal observed in the heart.

The paper by Lapa et al. (2) parallels these findings in patients 5 to 10 days after acute MI. ^{68}Ga-pentixafor PET signal in the infarct, which was identified by delayed Gd enhancement magnetic resonance imaging, was observed in 3 of 7 investigated patients. Taken together, both studies indicate specific uptake in some infarcted segments, no uptake in other infarcted segments, and agree that the remote, noninfarcted myocardium shows low PET signal.

How cell-specific is ^{68}Ga-pentixafor? The data from blocking experiments (3) suggest specificity for CXCR4, which is quite widely expressed by different leukocytes. These include tissue resident macrophages, circulating neutrophils and monocytes, lymphocytes, and hematopoietic progenitors (10). Some reports (11,12) describe expression of CXCR4 by cardiomyocytes and cardiac fibroblasts. The healthy, but particularly the ischemic myocardium, contains a robust number of leukocytes (7). The typical methods to isolate cardiomyocytes and cardiac fibroblasts do not involve antigen-specific cell sorting. The resulting stromal cell population is thus likely contaminated with infiltrating leukocytes and/or tissue resident macrophages, which express high levels of CXCR4. Close examination of immunoreactive histology (13) suggests that the receptor is, at least in some cases, expressed by noncardiomyocytes. Thus, evidence for the expression of the chemokine receptor by cardiomyocytes is less compelling. In addition, Thackeray et al. (3) used permanent LAD occlusion in mice. Four days after MI, ischemia has killed most myocytes in the infarct zone, where the agent uptake was high. The current studies do not definitely answer which cells are targeted by ^{68}Ga-pentixafor, although the associative flow cytometry data (3) and the previously reported time course of leukocyte infiltration into the infarct (7) suggest that leukocytes may indeed be the primary cardiac PET signal source.

The puzzling observation of heterogeneity, i.e., ^{68}Ga-pentixafor enrichment in 3 of 7 patients or 55 of 204 ischemic myocardial segments, provides food for thought and is potentially exciting because the method clearly distinguishes patient subgroups in a seemingly homogeneous cohort. It is now of paramount importance to identify whether the cardiac ^{68}Ga-pentixafor PET signal predicts post-MI recovery. One hypothetical scenario posits that only patients with a high number of recruited inflammatory neutrophils and monocytes showed ^{68}Ga-pentixafor uptake, whereas myocardial segments that are undergoing resolution of inflammation, with declining neutrophil numbers, did not. The observation that the PET signal was higher at earlier times and in severely injured segments, and lowered by angiotensin-converting enzyme–inhibitor therapy which decreases myocardial leukocyte levels (13),

supports this line of thought. If this hypothetical scenario is true, ^{68}Ga-pentixafor PET imaging may identify patients at risk for post-MI heart failure, and the method could be used to study the cardiac effects of anti-inflammatory interventions aiming at the prevention of post-MI remodeling.

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